PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
GARY J. CONNELL
SHERIDAN ROSS P.C.
1560 BROADWAY, SUITE 1200
DENVER, CO 80202

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 OCT 2008
Applicant's or agent's file reference 5941-79-1-PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day month year)*	Priority date *(day month year)*
PCT/US 08/70924	23 July 2008 (23.07.2008)	23 July 2007 (23.07.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/498; A61K 31/4406 (2008.04)
USPC - 514/266.24; 514/357

Applicant THE REGENTS OF THE UNIVERSITY OF COLORADO

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	25 September 2008 (25.09.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/70924

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/70924

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 11-61

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 11-61 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 11-61 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 11-61

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/70924

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-10	YES
	Claims	none	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-10	NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims	none	NO

2. Citations and explanations:

Claims 5-7 lack an inventive step according to PCT Article 33(3) as obvious over the article entitled 'Restoring E-Cadherin Expression Increases Sensitivity to Epidermal Growth Factor Receptor Inhibitors in Lung Cancer Cell Lines' by Witta et al. (hereinafter 'Witta'), in view of the publication 'Modulation of Histone Acetylation by [4-(Acetylamino)-N-(2-Amino-phenyl) Benzamide] in HCT-8 Colon Carcinoma' by Kraker et al. (hereinafter 'Kraker').

As to claim 5, Witta teaches a method for more effectively treating a cancer of epithelial origin (p 944, abstract - 'lung cancer') comprising administering to a patient a combination of at least one HDAC inhibitor and at least one epidermal growth factor receptor (EGFR) inhibitor (p 944, abstract - 'combined HDAC inhibitor and gefitinib treatment'). Witta does not teach wherein the HDAC inhibitor is not SAHA, MS-275, PXD-I-I(PDX-10I), LAQ-824, or TSA. However, Kraker teaches an HDAC inhibitor which is not SAHA, MS-275, PXD-I-I(PDX-10I), LAQ-824, or TSA (p 401, abstract - 'Here, we show that CI-994 is a histone deacetylase (HDAC) inhibitor that causes histone hyperacetylation in living cells'). A skilled artisan would have readily appreciated that CI-994, like MS-275, is in the benzamide class of HDAC inhibitors among the several different classes of HDAC inhibitors, and would have recognized that the close similarity in structure between the two means that they share the same mechanism of action and target sites among the different histones. Consequently, it would have been obvious to one of ordinary skill in the art to combine the teaching of Witta concerning circumventing EGFR inhibitor resistance in cancers of epithelial origin by combination treatment of EGFR inhibitor with MS-275 (Witta p 944, abstract), with the teaching of Kraker concerning CI-994 as another benzamide HDAC inhibitor (Kraker p 401, abstract), and to substitute the CI-994 for MS-275 in the combination treatment of a cancer of epithelial origin, such as lung cancer, because the two molecules share similar structure and therefore similar targets and mechanism of action.

As to claim 6, Witta teaches a method for more effectively treating a cancer of epithelial origin (p 944, abstract - 'lung cancer') comprising administering to a patient a combination of at least one HDAC inhibitor and at least one epidermal growth factor receptor (EGFR) inhibitor (p 944, abstract - 'combined HDAC inhibitor and gefitinib treatment'). Witta does not teach that the HDAC inhibitor is CI-994. However, Kraker teaches the HDAC inhibitor CI-994 (p 401, abstract - 'Here, we show that CI-994 is a histone deacetylase (HDAC) inhibitor'). A skilled artisan would have readily appreciated that CI-994, like MS-275, is in the benzamide class HDAC inhibitors among the several different classes of HDAC inhibitors, and would have recognized that the close similarity in structure between the two means that they share the same mechanism of action and target sites among the different histones. Consequently, it would have been obvious to one of ordinary skill in the art to combine the teaching of Witta concerning circumventing EGFR inhibitor resistance in cancers of epithelial origin by combination treatment of EGFR inhibitor with MS-275 (Witta p 944, abstract), with the teaching of Kraker concerning CI-994 as another benzamide HDAC inhibitor (Kraker p 401, abstract), and to substitute the CI-994 for MS-275 in the combination treatment of cancer of epithelial origin, such as lung cancer, because the two molecules share similar structure and therefore similar targets and mechanism of action.

As to claim 7, Witta does not expressly teach wherein the EGFR inhibitor is administered in an amount less than the amount of EGFR inhibitor that is administered without the HDAC inhibitor. However, this element would have been obvious to one of ordinary skill in the art because Witta does teach that an amount of EGFR inhibitor (p 948, Fig 5 - 'gefitinib') administered in combination with a HDAC inhibitor (p 948, Fig 5 - 'MS-275') is far more potent in causing apoptosis than administration of an identical amount of EGFR inhibitor alone (p 948, Fig. 5). Therefore, it would have been obvious to an ordinarily skilled artisan that a smaller amount of EGFR inhibitor, when administered in combination with an HDAC inhibitor, is required to exactly mimic the effects of the EGFR inhibitor administered alone.

Claims 8-10 lack an inventive step according to PCT Article 33(3) as obvious over the article entitled 'Histone Deacetylase Inhibitor LAQ824 Both Lowers Expression and Promotes Proteasomal Degradation of Bcr-Abl and Induces Apoptosis of Imatinib Mesylate-sensitive or -refractory Chronic Myelogenous Leukemia-Blast Crisis Cells' by Nimmanapalli et al. (hereinafter 'Nimmanapalli'), in view of the article entitled 'Imatinib mesylate (Gleevec) inhibits ovarian cancer cell growth through a mechanism dependent on platelet-derived growth factor receptor alpha and Akt inactivation,' by Matei et al. (hereinafter 'Matei').

----------Please see continuation in supplemental box----------

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/70924

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V Citations and Explanations

As to claim 4, Witta teaches a method for treating cancer in a patient comprising administering to a patient a combination of MS-275 and at least one epidermal growth factor receptor (EGFR) inhibitor (p 944, abstract). Witta does not expressly teach wherein the cancer is head and neck cancer. However, this element would have been obvious to one of ordinary skill in the art for the reasons setforth in claim 1. Specifically, there are close parallels between lung cancer and head and neck cancer. Mendelsohn teaches that head and neck cancer of epithelial origin (p 2787, abstract) and like other cancers of epithelial origin, is responsive to EGFR inhibitor therapy (p 2787, abstract). An ordinarily skilled artisan would have readily appreciated that E-cadherin expression is downregulated not only lung or breast cancer cells, as taught by Witta and Eger respectively, but in all cancer cells of epithelial origin, including head and neck cancers. This would have provided a motive for combination treatment of head and neck cancer with MS-275 and EGFR inhibitor to circumvent and enable effective treatment of EGFR resistant cancer cells .

Claims 1-10 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or utilized in industry.